

2016-09

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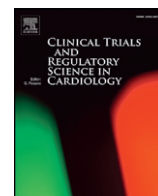
<http://hdl.handle.net/10026.1/11114>

10.1016/j.ctrsc.2016.06.001

Clinical Trials and Regulatory Science in Cardiology

Elsevier

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Effects of pre-procedural remote ischaemic pre-conditioning on the outcomes of elective percutaneous coronary intervention. A systematic review and meta-analysis

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ARTICLE INFO

Article history:

Received 25 April 2016

Received in revised form 15 June 2016

Accepted 25 June 2016

Available online 7 July 2016

Keywords:

Remote ischemic pre-conditioning

Elective percutaneous intervention

Major adverse cardiac events

Acute kidney injury

ABSTRACT

Objectives: Trials of remote ischemic pre-conditioning (RIPC) have suggested this intervention reduces complications of percutaneous coronary intervention and coronary by-pass surgery. The aims of this work were to (i) conduct a systematic review and meta-analysis of the effects of RIPC on cardiac and renal damage in patients undertaking elective percutaneous coronary intervention (PCI); (ii) summarize the results in an evidence-based clinical context.

Methods: We conducted a systematic search of published randomized controlled trials of RIPC for elective PCI up until May 1st, 2015. Studies of peri- or post-ischemic conditioning or emergency PCI were excluded.

Results: Nine studies, totalling 1253 patients were included. Compared to control, RIPC groups exhibited reduced peri-procedural myocardial infarction (MI) Odds Ratio (OR) 0.72 (95% CI 0.54 to 0.97, $p = 0.03$); ST-segment deviation OR 0.42 (95% CI 0.28 to 0.63, $p < 0.0001$); major adverse cardiac events (MACE) OR 0.41 (95% CI 0.21 to 0.84, $p = 0.01$); and acute kidney injury (AKI) OR 0.47 (95% CI 0.26 to 0.86, $p = 0.01$), but not mortality OR 1.00 (95% CI 0.27 to 3.73, $p = 1.00$).

Conclusions: RIPC is likely to prevent major adverse cardiac and renal events in patients undertaking elective PCI.

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1. Introduction

Coronary artery disease (CAD) is associated with the development of atherosclerotic plaques in the coronary arteries. Percutaneous coronary intervention (PCI) is one of the major treatment options used to relieve CAD symptoms, prevent myocardial infarction and in the immediate treatment of myocardial infarction. Unfortunately re-opening of a previously partially or completely occluded coronary vessel exposes the myocardium to ischemia reperfusion injury.

Remote ischaemic pre-conditioning (RIPC) relates to short sequences of ischemia, usually 4–5 min, of repeated blood pressure cuff inflation and deflation on a limb. Short periods of ischemia trigger cellular signalling pathways that protect against a subsequent longer period of ischemia, such as during PCI. RIPC is one of the most effective techniques of protecting the heart against ischemia reperfusion injury. The

RIPC process usually involves 3–4 cycles of repeated inflation-deflation lasting about 25–30 min [1]. RIPC has become increasingly attractive because it is relatively simple to administer and is non-invasive. Moreover, RIPC can be administered during natural waiting periods as patients enter the catheter lab for PCI. RIPC has been used in both upper and lower limbs and offers cardio-protection for those undergoing percutaneous coronary revascularization [2]. RIPC has also been found to reduce acute kidney injury in those exposed to contrast media [3] and infarct size by administering RIPC during transport to the medical centre prior to cardiac surgery [4]. More recent work has examined the cumulative effects of repeated RIPC treatments to manage blood pressure [5], improve endothelial function and blood flow [6].

The effects of RIPC may extend beyond the tissues exposed to cuff occlusion, with recent reports suggesting a neuroprotective effect that improved tolerance to cerebral ischemia [7]. RIPC induced neuroprotection by attenuating adenosine 5'-monophosphate-activated protein kinase [8]. RIPC may therefore improve impaired cognitive function in those with known cardiovascular or metabolic disease [9].

Despite several studies showing statistically significant reductions in surrogate measures of infarct size [10], some clinicians remain ambivalent about the clinical significance of these findings [11]. Modelling of creatine kinase [12] and tumour necrosis factor alpha [13] have been used to quantify infarct size in those with ST-elevated myocardial

Abbreviations: AKI, acute kidney injury; CAD, coronary artery disease; IPC, ischemic pre-conditioning; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention; RIPC, remote ischaemic pre-conditioning; RCT, randomized controlled trial.

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¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

infarcts. Cardiac biomarkers are used as a cardiac risk stratification tool [14].

Recent meta-analyses examined the benefits of IPC for people undertaking PCI, but this work only assessed surrogate measures of myocardial infarct size and acute kidney injury and the latter of these analyses also considered non-elective PCI [15,16]. There are many other relevant RIPC outcome measures that have been reported for which data pooling has not yet been conducted. Other analyses combined data from studies of pre- and post-conditioning, but between study heterogeneity was high indicating data pooling of these two slightly different interventions may not be justified [17,18]. Despite these previous pooled analyses the clinical significance of RIPC remains in doubt as the findings have not been compared with published thresholds of clinical significance [19,20]. We have therefore taken the approach of limiting our analysis to remote-preconditioning only in those undertaking elective percutaneous intervention in order to minimize the confounding effects of varied study inclusion criteria and in the type of preconditioning stimulus.

The aims of this work were to; (i) examine the effects of RIPC on a range of major adverse cardiac events (MACE) and markers of myocardial and renal damage in patients undertaking elective PCI; (ii) relate these findings to established thresholds of clinical significance and provide an evidence based context for RIPC use.

2. Materials & methods

2.1. Search strategy

To identify potential studies systematic searches were carried out using the following databases: EMBASE, PubMed, Web of Science and the Cochrane Central Registry of Controlled Trials (CENTRAL). The search was supplemented by scanning the reference lists of eligible studies. The search strategy included the key concepts of “remote ischemic preconditioning” AND “percutaneous coronary intervention” (see supplementary Fig. S1). All identified papers were assessed independently by two reviewers. A third reviewer was consulted to resolve disputes. Searches of published papers were conducted up until May 1st, 2015.

2.2. Types of studies to be included

Only randomized controlled trials (RCTs) of RIPC in patients undergoing elective PCI were included. There were no language restrictions. Animal studies, review papers and non-randomized controlled trials were excluded. Studies that do not have any of the desired outcome measures or participants who were treated by other surgical modalities such as coronary artery bypass grafting were excluded. Incomplete data, or data from an already included study, were excluded. Studies that included interventions other than RIPC were excluded.

2.3. Participants/population

This meta-analysis analysed RCTs of both male and female adult (≥ 18 years) patients with coronary artery disease who were undergoing elective, but not emergency, PCI. Other treatment modalities and interventions for coronary artery disease such as RIPC in coronary artery bypass grafting were excluded.

2.4. Intervention(s), exposure(s)

This meta-analysis considered all RCTs where patients with stable angina or acute coronary syndrome being treated with PCI were exposed to RIPC. More specifically all RCTs where the intervention of expanding a blood pressure cuff or applying a medical tourniquet in a remote limb was carried out before PCI.

2.5. Comparator(s)/control

The meta-analysis utilised RCTs that compare RIPC during percutaneous coronary intervention with a usual care control group receiving sham or no RIPC during percutaneous coronary intervention.

2.6. Search Results

Our initial search found 486 articles. Of these 441 were excluded based upon title and abstract. Nineteen studies were excluded as they were not RCTs. Nine studies were excluded because they were trials of post-conditioning, one study was excluded because it was peri-conditioning and 7 studies were excluded because they were studies of emergency PCI (see supplementary Fig. S2). Nine studies [2,21–26,28,29] were included in our analysis.

2.7. Outcome(s)

The primary outcomes analysed were:

1. Peri-procedural myocardial infarction (MI)
(This was defined differently in the different trials. Ahmed et al. [21] and Xu et al. [22] defined MI as an increase in cTnT as greater than three times the 99th percentile URL, whilst Hoole et al. [23] used the same parameters for cTnI. Ghaemian et al. [24] and Prasad et al. [25] considered MI as cTnT >0.03 ng/ml. Liu et al. [2] did not report how they defined MI. Luo et al. [26] defined MI as cTnI >0.2 mg/ml).
2. ST segment deviation
(This was defined as either an elevation or depression of the ST segment on an ECG of >1 mm).
3. Incidence of post-PCI major adverse cardiac events (MACE) at 6 months
(Ghaemian et al. [24] defined this as hospitalization for acute coronary syndrome, MI, or death due to MI. Hoole et al. [23] defined this as hospital admissions with unstable angina/acute coronary syndrome, MI, heart failure, and stroke/transient ischemic attack. Liu et al. [2] defined this as cardiac death, hospital admissions with unstable angina/acute coronary syndrome, MI, heart failure and stroke/transient ischemic attack.)
4. Mortality
5. Acute kidney injury
(Defined as an increase in serum creatinine of $\geq 25\%$ above baseline).
6. C-reactive protein
7. Troponin T
(Measured at 16 h post PCI in Ahmed et al. [21]. Ghaemian et al. [24] measured this at 12 h and 24 h post PCI with the 24 h measurement used in this study. Prasad et al. [25] measured this at 8, 16 and 24 h post PCI with the 24 h measurement used in this study.)

2.8. Risk of bias (quality) assessment

The PEDro scale was used to assess study quality and reporting [27].

2.9. Strategy for data synthesis

Odds ratios will be calculated for dichotomous data. Meta-analyses will be completed for continuous data by calculating the mean difference between intervention and control groups from post-intervention data only. It is an accepted practice to only use post-intervention data for meta-analysis, but this method assumes that random allocation of participants always creates intervention groups matched at baseline for age, disease severity. In the case of elective PCI this will be true as negligible levels of creatine kinase etc. would be expected at baseline prior to elective PCI; hence we have excluded emergency PCI studies. All analyses were conducted using Revman 5.0 (Nordic Cochrane Centre Denmark). A fixed effects inverse variance model was used unless

heterogeneity was >75%, then a random effects model was used. Heterogeneity was quantified using the Cochrane Q test. We used a 5% level of significance and 95% confidence intervals; figures were produced using Revman 5.3.

3. Results

The nine studies [2,21–26,28,29] included in the analyses had an aggregate of 1253 participants, 630 of which received RIPC and 623 were control/sham group participants. Table 1 summarizes the characteristics of the included studies. Table S1 lists the excluded RCTs and reasons for exclusion. Seven studies used a sham control group, as opposed to usual care. Only one study utilized the lower limb for RIPC. The RIPC protocols were very similar in terms of periods of cuff occlusion and periods of reperfusion.

Table 1
Characteristics of included studies.

Study	RIPC protocol	Comparator	N RIPC (control)	Population	Age RIPC (control)	Male % RIPC (control)	All outcome measures
Ahmed et al. 2013 Egypt	Upper limb 3 × 5 min & 5 min reperfusion	Sham RIPC (deflated cuff)	77 (72)	Elective PCI	54.6 ± 7.8 (53.5 ± 8.8)	87 (86)	CK-MB Troponin T CRP Procedural MI Acute kidney injury Creatinine Cystatin C Urinary NGAL Mortality Procedural MI Troponin T Intra-procedural arrhythmia ST-segment deviation MACE Mortality Troponin I CRP ST-segment deviation MACCE Procedural MI Creatinine GFR
Er et al. 2012 Germany	Upper limb 4 × 5 min & 5 min reperfusion	Sham RIPC (10 mm Hg)	50 (50)	Elective PCI	73.2 ± 9.1 (72.7 ± 11.4)	68 (74)	CK CK-MB Troponin I CRP ST-segment deviation MACE Mortality Troponin I Procedural MI Creatinine GFR
Ghaemian et al. 2012 Iran	Lower limb 2 × 5 min & 5 min reperfusion	Sham RIPC (deflated cuff)	40 (40)	Elective PCI	58.8 ± 9.8 (61 ± 9.8)	40 (55)	CK CK-MB Troponin I CRP ST-segment deviation MACE Mortality Troponin I Procedural MI Creatinine GFR
Hoole et al. 2009 UK	Upper limb 3 × 5 min & 5 min reperfusion	Sham RIPC (deflated cuff)	104 (98)	Elective PCI	63.2 (61.8)	81 (76)	CK CK-MB Troponin I CRP ST-segment deviation MACE Mortality Troponin I Procedural MI Creatinine GFR
Iliodromitis et al. 2006 Greece	Upper limb 3 × 5 min & 5 min reperfusion	Sham RIPC (deflated cuff)	20 (21)	Elective PCI	61 ± 10 (62 ± 8)	Not given	CK CK-MB Troponin I CRP ST-segment deviation MACE Mortality Troponin I Procedural MI Creatinine GFR
Liu et al. 2014 China	Upper limb 3 × 5 min & 5 min reperfusion	Sham RIPC (deflated cuff)	98 (102)	Elective PCI	59.9 ± 16.2 (56.3 ± 14.3)	48 (61)	CK CK-MB Troponin I CRP ST-segment deviation MACE Mortality Troponin I Procedural MI Creatinine GFR
Luo et al. 2013 China	Upper limb 3 × 5 min & 5 min reperfusion	No RIPC	101 (104)	Elective PCI	59.2 ± 10.3 (59.3 ± 9.5)	77 (75)	CK CK-MB Troponin I CRP ST-segment deviation MACE Mortality Troponin I Procedural MI Creatinine GFR
Prasad et al. 2013 USA	Upper limb 3 × 3 min & 3 min reperfusion	Sham RIPC (10 mm Hg)	47 (48)	Elective PCI	67.2 ± 11.4 (65.1 ± 11)	91 (75)	CK CK-MB Troponin I CRP ST-segment deviation MACE Mortality Troponin I Procedural MI Creatinine GFR
Xu et al. 2014 China	Upper limb 3 × 5 min & 5 min reperfusion	No RIPC	102 (98)	Elective PCI	69.1 ± 3.8 (68.9 ± 2.9)	66 (70)	CK CK-MB Troponin I CRP ST-segment deviation MACE Mortality Troponin I Procedural MI Creatinine GFR

CK – creatine kinase; CRP – C-reactive protein; EPC – endothelial progenitor cells; GFR – glomerular filtration rate; MACE – major adverse coronary events; MI – myocardial infarction; PCI – percutaneous coronary intervention; RIPC – remote ischaemic pre-conditioning; Urinary NGAL – urinary neutrophil gelatinase-associated lipocalin.

3.1. Peri-procedural myocardial infarction and ST-segment deviation

Seven studies reported the incidence of peri-procedural myocardial infarction (MI), the odds ratio for the pooled analysis of RIPC versus control group was 0.72 (95% CI 0.54 to 0.97, $p = 0.03$) suggesting a 28% reduced risk of MI in patients receiving RIPC (see Fig. 1). These findings were supported by reductions in ST-segment deviation, as the odds ratio for the pooled analysis of RIPC versus control group was OR 0.42 (95% CI 0.28 to 0.63, $p < 0.0001$) suggesting a 58% reduction in prevalence of ST-segment deviation in patients receiving RIPC (see Fig. 2).

3.2. Major adverse coronary events at 6 months

Three studies reported the incidence of major adverse cardiac events (MACE), the odds ratio for the pooled analysis of RIPC versus control

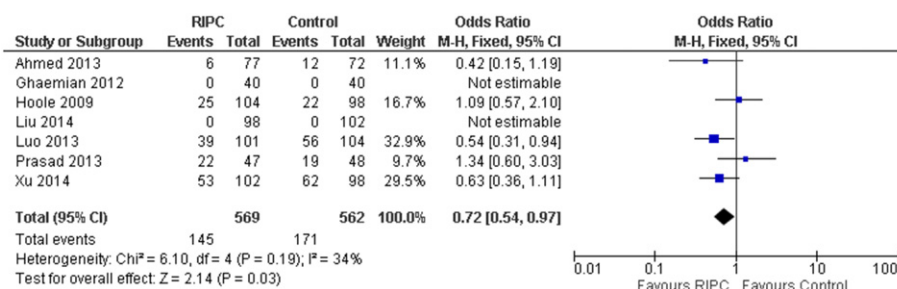


Fig. 1. Peri-procedural myocardial infarction.

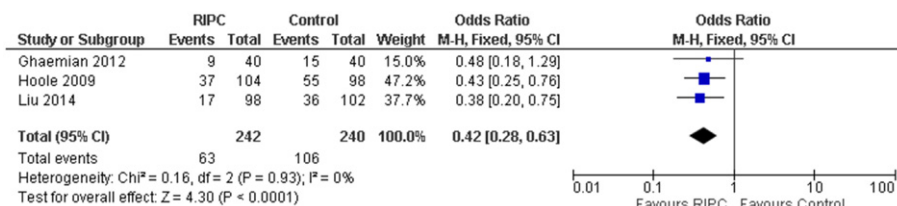


Fig. 2. ST-segment deviation.

group was OR 0.41 (95% CI 0.21 to 0.84, $p = 0.01$) suggesting a 59% reduced risk of MACE in patients receiving RIPC (see Fig. 3).

3.3. Mortality

Five studies reported the mortality incidence, the odds ratio for the pooled analysis of RIPC versus control group was 1.00 (95% CI 0.27 to 3.73, $p = 1.00$) suggesting no significantly reduced risk of mortality in patients receiving RIPC (see Fig. 4).

3.4. Acute kidney injury

Four studies reported the incidence of acute kidney injury, the odds ratio for the pooled analysis of RIPC versus control group was 0.47 (95% CI 0.26 to 0.86, $p = 0.01$) suggesting a 53% reduced risk of acute kidney injury in patients receiving RIPC. (See Fig. 5).

3.5. Biomarkers of cardiovascular damage and inflammation

Troponin-T and C-reactive protein were not significantly different between RIPC and control groups (supplementary Figs. S3 and S4, respectively).

3.6. Assessment of study quality

We utilised the Physiotherapy Evidence database (PEDro) scale to evaluate study quality. Median Pedro score was 7 with 1 study scoring 9, 4 studies scoring 7, 3 studies scored 6 and 1 study scored 5 (Supplementary Table S2).

3.7. Publication bias and study heterogeneity

We assessed publication bias by Egger Plots. There was minimal evidence of bias. Study heterogeneity was assessed by Cochrane Q test, and was low in all cases except MACE, where it was moderate (51%).

4. Discussion

Our meta-analysis is the first to examine the benefits of remote ischemic pre-conditioning (RIPC) for people undertaking elective percutaneous coronary intervention for outcome measures other than myocardial infarct size and acute kidney injury. We found RIPC significantly reduced the risk of peri-procedural infarct, ST-segment deviation, major adverse cardiac events (MACE) and acute kidney injury. These

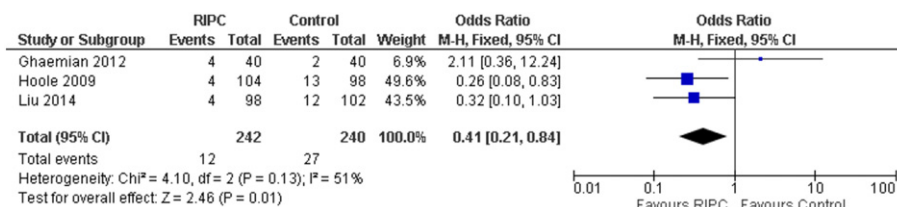


Fig. 3. Major adverse coronary events.

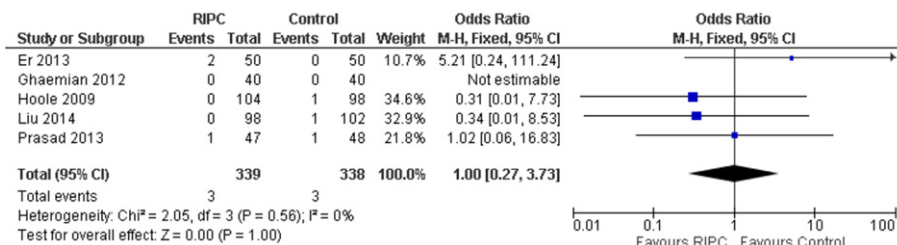


Fig. 4. Mortality.

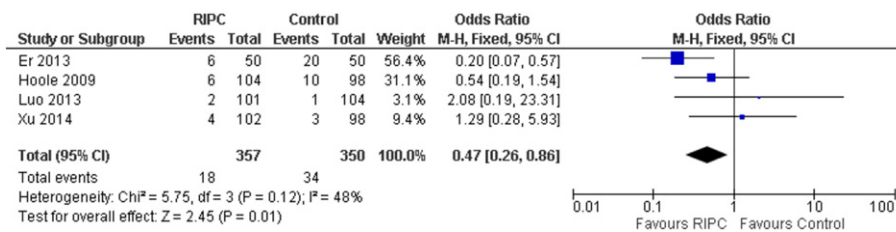


Fig. 5. Acute kidney injury.

findings provide evidence of a wider scope of benefits from RIPC than had been reported previously.

One of the dilemmas faced by patients confronted with the decision to undergo non-emergency (elective) PCI is to weigh up the potential risks of PCI against the likely stabilising benefits. Our work has shown that RIPC provides a likely mitigating effect for a variety of complications to elective PCI. Recent work has shown that PCI does not reduce post-intervention mortality risk as much as cardiac by-pass grafting (CABG), even after adjusting for confounders [30]. Risk of myocardial infarction (MI) during PCI has been estimated using cardiac biomarkers as about 8.6% (95% confidence intervals: 5.8% to 12.2%), with symptomatic ischemia in about 25% of MI patients [31]. Taking an evidence-based approach, our analyses suggest that the risk of MI could be reduced by 28% from 8.6% to 6.2%. These data imply that the number of patients needed to be treated to prevent 1 MI is <4. Prevalence data for MACE suggested 12% during PCI [32]. Our analyses suggest RIPC could reduce MACE during PCI by 59% to 7.1%.

While our analyses did not suggest a significantly reduced risk of mortality in patients receiving elective RIPC, this may be due to the small number of deaths reported in the included studies. In the RIPC groups 5 deaths were recorded, while in the sham/control groups 9 deaths were recorded. Intuitively, we are able to deduce two things from these data: First, the number of published deaths are too few currently for analyses to provide statistical significance. Second, the number of deaths in the non-intervention groups is almost twice that of the RIPC groups, this could be considered clinically significant even if it is not statistically significant.

Incidence of acute kidney injury (AKI) during PCI ranges from 6 to 26%, but depends on haemoglobin levels [33]. Using the reported conservative prevalence estimate of 6%, our analyses suggest RIPC could reduce AKI during PCI by 53% to 3.2%.

RIPC is inexpensive, not time-consuming and easily administered by staff with minimal training. In addition to the utilization of RIPC for PCI or CABG, several works have recently reported the use of repeated sessions of RIPC over 1–8 week periods, in order to manage blood pressure and improve blood flow [5,6]. We now await results of further trials that are in progress.

The primary limitation of this work is that relatively few adverse events exist in randomized, controlled trials reported in the published literature. A secondary limitation is that studies have used marginal techniques to establish if myocardial injury has occurred, rather than established techniques like cardiac MRI or repeated Troponins, or combinations of two or more methods.

5. Conclusions

Remote ischemic pre-conditioning (RIPC) provides clinically meaningful reductions in major adverse cardiac and renal events for people undertaking elective percutaneous coronary intervention. These findings provide evidence that only a small number of patients (<5) are required to prevent one adverse event, RIPC is therefore probably under-utilized.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ctrsc.2016.06.001>.

Source of funding

None.

Conflicts of interest

None.

Acknowledgements

None declared.

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